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CPAP increases exercise tolerance in obese subjects with obstructive sleep apnea

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Summary
Obese subjects commonly suffer from exertional dyspnea and exercise intolerance. Preliminary evidence suggests that treatment with nocturnal continuous positive airway pressure (nCPAP) may improve dyspnea in obese patients with obstructive sleep apnea (OSA), but the effect on exercise tolerance is unknown. This study sought to investigate whether nCPAP improves exercise tolerance and exertional dyspnea in obese patients with OSA.

Obese patients prescribed nCPAP for moderate/severe OSA and without cardiopulmonary disease were recruited. Patients completed a constant-load exercise test and Baseline and Transitional Dyspnea Index questionnaires (BDI/TDI) at baseline and after one and three months of nCPAP. Primary outcome was change in constant-load exercise time from baseline to one and three months. Secondary outcomes included changes in isotime dyspnea, isotime leg fatigue and BDI/TDI score at one and three months.

Fifteen subjects (body mass index = 43 kg m^{-2}, apnea-hypopnea index = 49·hr^{-1}) were studied. Constant-load exercise time increased by 2.0 min (40%, $p = 0.02$) at one month and 1.8 min (36%, $p = 0.04$) at three months. At one and three months, isotime dyspnea decreased by 1.4 ($p = 0.17$) and 2 units ($p = 0.04$), and leg fatigue decreased by 1.2 ($p = 0.18$) and 2 units ($p = 0.02$), respectively. BDI/TDI scores were 2.7 ($p = 0.001$) and 4.5 points ($p < 0.001$) at one and three months. Peak oxygen consumption and static pulmonary function were unchanged.

Nocturnal CPAP improves exercise tolerance and dyspnea in obese patients with OSA. Effects on exercise time and chronic dyspnea were seen after one and three months of nCPAP, while exertional dyspnea was only improved at three months.

Abbreviations: AHI, apnea-hypopnea index; ANOVA, analysis of variance; BDI/TDI, baseline dyspnea index/transitional dyspnea index; BMI, body mass index; IC, inspiratory capacity; MRC, Medical Research Council; nCPAP, nocturnal continuous positive airway pressure; OSA, obstructive sleep apnea; SD, standard deviation; VO_2, oxygen consumption.

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Introduction

Obesity is associated with multiple medical conditions, including metabolic, cardiopulmonary and musculoskeletal diseases,[1] and has been identified as an independent risk factor for premature death.[2] Obesity is an established risk factor for obstructive sleep apnea (OSA)[3] and has a number of profound effects on the cardiac and respiratory systems. It is well documented that obesity reduces static chest wall compliance and increases airway resistance due to respiration at lung volumes closer to residual volume.[4,5] These mechanical problems are worsened in the supine position.[6] Additionally, the hypercapnic ventilatory response is reduced in obese subjects compared to non-obese subjects.[7] Obesity also independently affects cardiovascular function by elevating pulmonary artery pressure and impairing left ventricular diastolic function.[8,9] These cardiopulmonary changes may have important implications for exercise intolerance in obese individuals.

Obesity is commonly associated with both a decreased exercise capacity[10] and an increase in oxygen cost of breathing during exercise.[11] Exertional dyspnea is also increased in obese subjects[12] and is a prime determinant of functional impairment.[13] The inability to sustain exercise due to dyspnea results in worsening obesity, deconditioning, and an increased risk of cardiovascular disease.[14,15]

The effects of OSA on exercise are variable. Although reductions in aerobic capacity have not been consistently demonstrated,[16–20] patients with OSA may have impaired cardiac stroke volume, inefficient ventilation during exercise and muscle metabolic impairment due to nocturnal hypoxemia.[21–23] Chronic nocturnal continuous positive airway pressure (nCPAP) has been shown to improve exercise capacity in small studies,[24,25] but the effect on dyspnea is unknown.

Clinical observation by our group suggests that obese patients with exertional dyspnea as a presenting symptom of OSA report an improvement in dyspnea after treatment with nCPAP, without a change in body mass index (BMI) or activity level. This reduction in dyspnea may translate into improved exercise tolerance; however, to date no study has addressed this interesting question. The aim of the current study was to test the hypothesis that nCPAP would reduce exertional dyspnea and improve exercise tolerance in obese patients with OSA.

Methods

Additional detail on the methods is provided in an online data supplement.

Patients

Subjects were recruited from referrals to the Foothills Medical Centre Sleep Centre in Calgary, Alberta, Canada. Inclusion criteria were: age 18–65 years; BMI $\geq$ 30 kg m^2; a new diagnosis of moderate to severe OSA (Apnea-Hypopnea Index (AHI) $\geq$ 15 h^{-1}); decision by the patient and sleep physician to use nCPAP for treatment of OSA; and Medical Research Council (MRC) class III or greater dyspnea. Exclusion criteria were: known or suspected airways or parenchymal lung disease; cardiac disease including pulmonary hypertension; active smoking within the last 6 months; previous treatment for OSA; inability to tolerate nCPAP; another sleep disorder; inability to perform cycle ergometry; or refusal or inability to provide informed consent. All subjects signed an informed consent that had received approval from the University of Calgary Conjoint Health Research Ethics Board.

Study design

This pilot study used a prospective, single group design. At baseline, subjects completed the dyspnea and physical activity questionnaires before performing a symptom-limited incremental exercise test. On a separate day, patients underwent constant-load exercise testing. The subjects were then started on nCPAP at a pressure determined by polysomnography. After one and three months of nCPAP, patients repeated both incremental and constant-load testing on separate days and completed the dyspnea and physical activity questionnaires. Pulmonary function measurements were repeated after three months. Investigators were blind to the results of all measurements until the conclusion of the study.

Specific methodology

Incremental cardiopulmonary exercise test

Incremental cardiopulmonary exercise testing to symptom limitation was performed according to American Thoracic Society guidelines.[26]

Constant-load exercise trials

A symptom-limited constant-load exercise trial was performed at 85% of maximal workload achieved in the baseline incremental exercise trial. Exertional symptoms using the modified Borg scale,[27] and repetitive inspiratory capacity (IC) maneuvers were performed every 2 min.

Measurements of dyspnea and physical activity

The Baseline Dyspnea Index/Transitional Dyspnea Index questionnaire (BDI/TDI) was used to assess changes in chronic dyspnea. The BDI is a baseline measure of chronic dyspnea, while the TDI quantifies the change from baseline. The Godin Leisure Time Exercise questionnaire was also used to account for activity as a possible contributor to increased exercise tolerance.[28]

Outcomes

The primary outcome was the change in constant-load exercise time from baseline to one and three months after the initiation of nCPAP. Secondary outcomes included the changes in isotime exertional symptoms and chronic exertional dyspnea from baseline to one and three months. Isotime was defined as the exercise time at symptom limitation during the shortest of the three constant-load trials.

Statistical analysis

One-way repeated measures analysis of variance (ANOVA) was used to compare primary and secondary outcomes at

baseline, one month and three months. Post-hoc comparisons were performed using Tukey's method. Linear regression was used to determine predictors of the primary and secondary outcomes. To examine the possible mechanisms for improved exercise tolerance, the relationships between mean Borg scores, oxygen consumption (VO_2) and ventilation were plotted for the baseline and three month incremental cardiopulmonary exercise tests, as previously described.[29] Comparison of these plots was performed using two-way repeated measures ANOVA. All statistics were performed using Intercooled Stata version 11 (StataCorp, College Station, TX). Values are represented as mean $\pm$ standard deviation (SD).

Results

The study patient flow is presented in Fig. 1. Recruitment took place between August 2007 and April 2009. Out of 87 patients who were screened, 27/87 (31%) were deemed eligible and consented to participate, and 23/27 (85%) started nCPAP. Fifteen subjects completed the study and were included in the primary analysis. There were no adverse events due to nCPAP or any of the study procedures.

Patient characteristics

Table 1 shows the baseline clinical characteristics for the study population. Fifteen subjects (six males, nine females) participated in the study. Mean age was 49 $\pm$ 6 years, with a mean BMI of 42.6 $\pm$ 8.8 kg m^{-2}. Mean BDI score was 6.9 $\pm$ 0.7. Mean peak VO_2 was 17.0 $\pm$ 4.2 mL/kg/min.

The effect of nocturnal CPAP on exercise tolerance and exertional symptoms

Table 2 shows baseline and follow-up physiologic data. Compared to baseline (5.1 $\pm$ 2.0 min), exercise time increased by 2.0 min (7.1 $\pm$ 4.7 min, $p = 0.02$) after one month of nCPAP and by 1.8 min (6.9 $\pm$ 3.8 min, $p = 0.04$) after three months of nCPAP (Fig. 2). There was no difference between the one month and three-month constant-load times. During this time, there was no change in BMI, leisure-time exercise, spirometry, diffusion capacity for carbon monoxide, blood pressure, peak VO_2, peak IC or oxyhemoglobin saturation. Average nCPAP usage was 5.8 $\pm$ 2 h, with a residual AHI of 4.7 $\pm$ 2.5 h^{-1}.

From baseline to one and three months, respectively, the isotime Borg dyspnea score decreased by 1.4 and 2.0 points (from 7.3 $\pm$ 2.4 to 5.9 $\pm$ 2.4 at one month ($p = 0.17$) and 5.3 $\pm$ 2.9 at three months ($p = 0.04$)), and the leg discomfort score decreased by 1.2 and 2.0 points (from 8.1 $\pm$ 2.3 to 6.9 $\pm$ 2.9 at one month ($p = 0.18$) and 6.1 $\pm$ 2.6 at three months ($p = 0.02$)). There was no significant change in isotime dyspnea or leg discomfort from one to three months. The Borg scores at symptom limitation did not change from baseline to one and three months, although they were reached after a longer duration of exercise (Fig. 3). There was no change in isotime minute ventilation, oxygen pulse or inspiratory capacity between baseline and three month testing. There was an association between constant-load exercise time and isotime dyspnea between baseline and one month ($R^2 = 0.43$, $p = 0.008$), which was also seen at three months ($R^2 = 0.45$, $p = 0.006$). There was no association between the change in exercise time or exertional symptoms and AHI, nocturnal

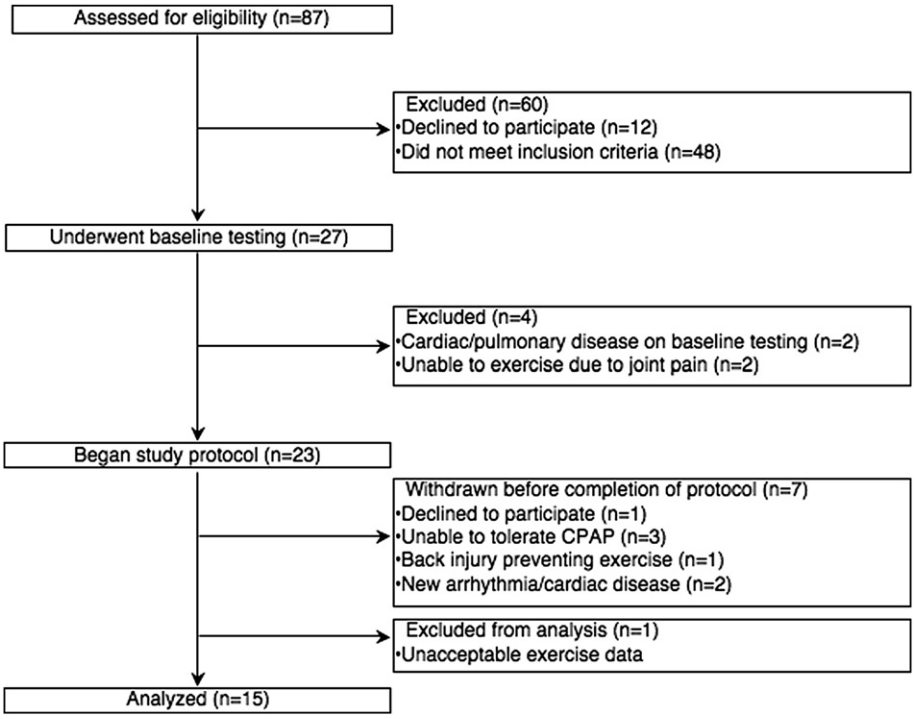

Figure 1 Study patient flow.

Table 1 Patient characteristics.

Characteristic	Value
Age (y)	49 ± 6
Subjects (M,F)	15 (6,9)
Body mass index (kg m^{-2})	42.6 ± 8.8
Apnea/hypopnea index (hr^{-1})	48.1 ± 33.1
Mean nocturnal oxygen saturation (%)	92.4 ± 2.1
% of night with $S_pO_2 < 90\%$	26.0 ± 25.8
nCPAP pressure (cm H_2O)	9.7 ± 2.8
MRC score	3.1 ± 1.2
Baseline dyspnea index score	6.9 ± 0.7
Epworth sleepiness score	15 ± 6

Definition of abbreviations: S_pO_2 = oxyhemoglobin saturation, nCPAP = nocturnal continuous positive airway pressure, MRC = Medical Research Council. Values are mean ± SD.

oxygen saturation, baseline Epworth Sleepiness Scale score (ESS) or change in ESS from baseline to three months.

The effect of nocturnal CPAP on chronic dyspnea

At one and three months, the respective TDI overall scores were 2.7 ± 2.3 ($p = 0.001$ for difference from 0) and 4.5 ± 2.9 ($p < 0.001$). Improvements in dyspnea were seen in all three components of the TDI. There was a trend toward a reduction in MRC class (3.0—2.5, $p = 0.054$). There was no difference in metabolic equivalents using the Godin Leisure Time Exercise questionnaire. The ESS improved from 15 at baseline to 6 at the three month follow-up assessment.

Relationships between exertional symptoms, oxygen consumption and ventilation

Fig. 4 shows the plotted graphs of exertional symptoms at varying mean levels of VO_2 and ventilation. There was a trend to reduction in mean Borg dyspnea scores at peak VO_2 from baseline to three months ($p = 0.068$). Mean Borg leg discomfort was similar at all levels of VO_2. At ventilation above 50 L/min, there was also a trend towards a lower mean Borg dyspnea score at three months compared to baseline ($p = 0.078$).

Discussion

The principal novel finding of this study is that nCPAP improves constant-load exercise time in obese subjects with OSA and dyspnea as a presenting complaint. This effect was seen one and three months after nCPAP initiation. The improvement in exercise time was accompanied by reductions in isotime measurements of exertional dyspnea and leg fatigue. Additionally, measures of chronic dyspnea were also improved with this intervention. These results occurred without changes in BMI, pulmonary function, physical activity or fitness. Our findings support the study hypothesis that nCPAP improves dyspnea and exercise tolerance in this population of patients.

Table 2 Physiologic data.

Measurement	Baseline		1-Month follow-up		3-Month follow-up	
	Value	% Predicted	Value	% Predicted	Value	% Predicted
FVC (L)	3.72 ± 0.85	99	—	—	3.73 ± 0.85	98
FEV_1 (L)	2.95 ± 0.72	97	—	—	2.9 ± 0.67	96
DL_{CO} (mL/mmHg/min)	27.34 ± 6.76	89	—	—	27.97 ± 5.88	90
Peak VO_2 (mL/min)	2108 ± 602	103	2081 ± 507	103	2090 ± 532	105
Peak VO_2 (mL/kg/min)	17.0 ± 4.2	60	16.5 ± 3.5	59	16.6 ± 3.5	59.2
Peak workload (W)	126 ± 36	—	118 ± 34	—	124 ± 30	—
Peak heart rate (bpm)	136 ± 19	79	137 ± 21	80	136 ± 18	80
Peak O_2 pulse (L)	15.7 ± 3.8	124	15.3 ± 3.5	122	15.3 ± 3.6	123
Peak blood pressure (mmHg)	181/98 ± 33/10	—	184/94 ± 26/8	—	185/96 ± 32/13	—
Peak ventilation ($L\ min^{-1}$)	72 ± 24	66	73 ± 19	66	73 ± 21	68
Peak IC (L)	3.05 ± 0.83	—	2.99 ± 0.67	—	3.05 ± 0.83	—

Definition of abbreviations: FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 s, DL_{CO} = diffusion capacity of the lung for carbon monoxide, VO_2 = oxygen consumption, IC = inspiratory capacity. Values are mean ± SD.

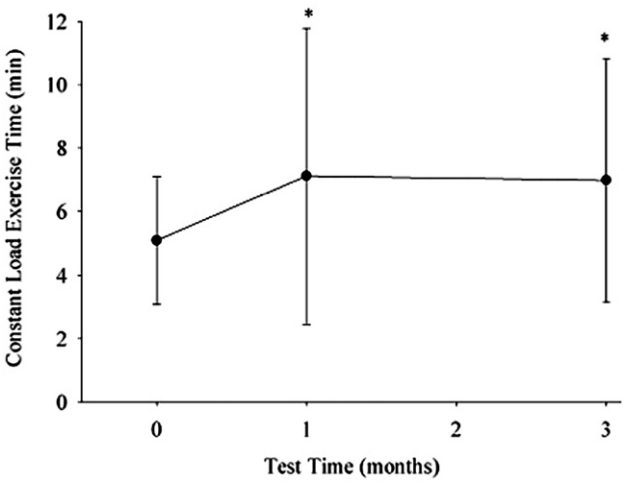

Figure 2 Exercise time during constant-load exercise at baseline and after one and three months of nCPAP. Values represent mean ± SD, $*p < 0.05$.

To our knowledge, this is the first study to investigate whether dyspnea and exercise intolerance experienced by obese subjects with OSA can be improved with nCPAP; thus, it is difficult to compare our findings to previous work in this area. Lin and colleagues demonstrated improvements in peak VO_2, anaerobic threshold, peak workload, oxygen pulse and ventilation at maximal exercise after two months of nCPAP therapy in 20 subjects with OSA.[25] Alonso-Fernandez *et al.* showed a reduced stroke volume response to exercise in 31 OSA patients compared to 15 control subjects, and demonstrated the reversal of this phenomenon after 3 months of nCPAP.[21] In contrast to the present investigation, these studies included non-obese subjects with abnormal right or left ventricular function at baseline, and did not include patients with dyspnea as a presenting complaint. Additionally, these authors did not measure physical activity between cardiopulmonary exercise tests, which could have confounded their results.

There are a number of potential mechanisms for the increase in constant-load exercise time demonstrated in this cohort. Nocturnal CPAP may confer mechanical benefits to the respiratory system. At rest and during exercise, obesity increases the mechanical load on the respiratory system through a reduction in chest wall compliance and due to increased intrinsic positive end expiratory pressure from expiratory flow limitation.[4,29,30] Consequently, the functional residual capacity in obese subjects is reduced.[31] The supine position worsens these mechanical limitations in obese subjects,[4,6] which could result in lower lung volumes and micro-atelectasis during sleep. Acute CPAP has been shown to reduce atelectasis in obese subjects[32] but to our knowledge there are no studies examining the effect of nCPAP on respiratory mechanics. Our study showed a trend toward a decreased Borg dyspnea score for a given ventilation, supporting a mechanical cause of improved exertional dyspnea with nCPAP. The reduction in exertional

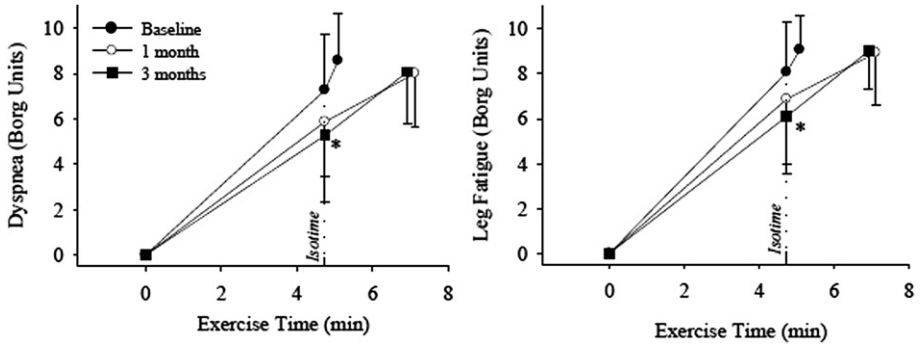

Figure 3 Dyspnea and leg fatigue during constant-load exercise at baseline and after one and three months of nCPAP. Values represent mean ±SD, $*p < 0.05$.

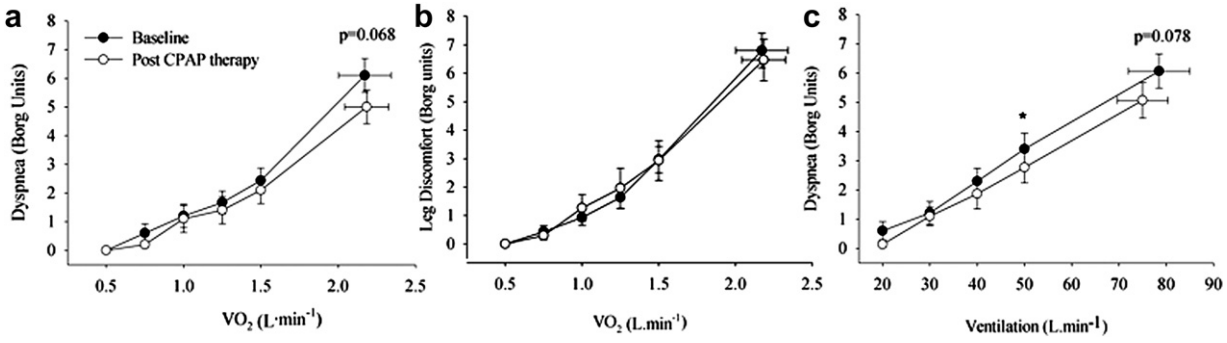

Figure 4 Relationship between a) exertional dyspnea and oxygen consumption (VO_2), b) exertional leg discomfort and VO_2, c) exertional dyspnea and ventilation at baseline and after three months of nCPAP. Values represent mean ±SE, $*p < 0.05$.

dyspnea was associated with an increase in exercise time, providing a link between the mechanical benefits of nCPAP and the improvement in exercise tolerance.

The cardiovascular benefits of nCPAP have been demonstrated using imaging and clinical measurements. Studies of OSA patients using Doppler echocardiography have demonstrated depressed myocardial contractile reserve[33] and impaired left and right ventricular performance despite a normal ejection fraction.[34] In patients with OSA, as assessed by cardiac magnetic resonance imaging, nCPAP improved right ventricular end diastolic and systolic volumes without an appreciable change in left ventricular size or function.[35] nCPAP has also been shown to reduce arterial stiffness, mean peripheral arterial pressure and central blood pressure in patients with newly diagnosed OSA, and a deterioration in these parameters was seen following nCPAP withdrawal.[36] We examined oxygen pulse during exercise as a surrogate of stroke volume, and mean arterial pressure during exercise. Neither of these measures changed with nCPAP, suggesting the absence of a cardiovascular benefit of nCPAP. Additionally, there was no change seen in the Borg leg fatigue-VO_2 relationship, suggesting that nCPAP did not improve oxygen delivery in these patients. As such it appears that the improvements in exercise tolerance are a result of improved pulmonary mechanics rather than cardiovascular adaptations.

There are a couple of limitations to the present study that need to be acknowledged. First, we did not randomize patients to a separate control group as the primary aim was to "prove-the-principle" that nCPAP could improve dyspnea and exercise tolerance in obese patients with OSA before performing a much more complex and expensive randomized trial. Second, while we demonstrated an increase in exercise tolerance with nCPAP, our study did not seek to delineate whether this beneficial effect was due to improvements in mechanical dysfunction related to obesity, cardiopulmonary perturbations of OSA, or a combination of both. Further studies are now needed to clearly identify the mechanism responsible for the improvements in dyspnea and exercise tolerance with nCPAP in this population.

In conclusion, the findings of this pilot study demonstrate that three months of nCPAP can improve exertional dyspnea and exercise tolerance in obese patients with OSA. This study has important clinical implications. With greater exercise tolerance, obese patients would be able to exercise more, promoting weight loss as a management strategy for OSA. Weight loss and increased physical activity could also have more general health benefits such as cardiovascular risk reduction. Further studies are now warranted to definitively address these questions.

Conflict of interest statement

Dr. Pendharkar has received compensation from Respiratory Homecare Solutions, Inc. for the interpretation of Level III sleep studies. Dr. Tsai has received compensation from Respiratory Homecare Solutions, Inc., Vitalaire Canada and Medigas for the interpretation of Level III sleep studies. Dr. Eves has no conflicts of interest to disclose. Dr. Ford has no conflicts of interest to disclose. Dr. Davidson has no conflicts of interest to disclose

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.rmed.2011.06.007.

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